DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-758/SLR-036

Novartis
Attention: Susan Witham
59 Route 10
East Hanover, NJ 07936

AUG 9 1998

Dear Ms. Witham:

Please refer to your supplemental new drug application dated November 20, 1997, received November 24,1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Clozaril (clozapine) tablets.

We acknowledge receipt of your submission dated July 1, 1998. Your submission of July 1, 1998, constituted a full response to our April 17, 1998 action letter.

This supplemental new drug application provides for the following labeling changes:

1. **PRECAUTIONS** section -- A cautionary statement regarding concurrent use of Clozaril and selective serotonin reuptake inhibitors (SSRI's) was added. As agreed in the telephone conversation of August 7,1998, between yourself and Steve Hardeman, of this Division, we have amended the SSRI cautionary statement to read as follows:

   "In a study of schizophrenic patients who received clozapine under steady state conditions, fluvoxamine or paroxetine was added in 16 and 14 patients, respectively. After 14 days of co-administration, mean trough concentrations of clozapine and its metabolites, N-desmethylclozapine and clozapine N-oxide, were elevated with fluvoxamine by about three-fold compared to baseline concentrations. Paroxetine produced only minor changes in the levels of clozapine and its metabolites. However, other published reports describe modest elevations (less than two-fold) of clozapine and metabolite concentrations when clozapine was taken with paroxetine, fluoxetine, and sertraline. Therefore, such combined treatment should be approached with caution and patients should be monitored closely when Clozaril (clozapine) is combined with these drugs, particularly with fluvoxamine. A reduced Clozaril (clozapine) dose should be considered."

2. **CONTRAINDICATIONS** section-- Added statement that use -in patients with a previous hypersensitivity to clozapine or any other component of the drug is contraindicated.

3. **WARNINGS** section -- Added to Agranulocytosis subsection statistics for experience in the U.S. with Clozaril-associated agranulocytosis.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and

effective for use as recommended in the submitted labeling (November 20,1997).

Accordingly, the supplemental application is approved effective on the date of this letter. The above revisions are terms of the approval. Marketing the product before making the revisions, exactly as requested, in the product's final printed labeling (FPL) may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 19-758/SLR-036." Approval of this submission by FDA is not required before the labeling is used.

If additional information relating to the safety or effectiveness of this drug becomes available before we receive the final printed labeling, revision of that labeling may be required.

If a letter communicating important information about this drug product (i.e., a "Dear Healthcare Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Steve Hardeman, R.Ph., Regulatory Management Officer, at (301) 594-5533.

Sincerely,

8/18/98

Paul Leber, M.D.
Director
Division of Neurophamracological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research